c) determining an efficiency of detector primer extension, and;
d) detecting the presence or absence of the single nucleotide polymorphism based on the efficiency of detector primer extension.

14 (Amended) The method of Claim 13 wherein the amplification reaction is selected from the group consisting of SDA, 3SR, NASBA, and TMA.

20. (Amended) The method of Claim 19 wherein the label is a fluorescent donor/quencher dye pair and an increase in donor dye fluorescence is detected as an indication of the presence of the single nucleotide polymorphism.

Please add the following new Claim 63.

63. (New) A method for detecting a single nucleotide polymorphism in a target comprising:
a) hybridizing a detector primer and a second primer to the target such that extension of the second primer by polymerase displaces the detector primer from the target sequence, wherein the detector primer comprises a diagnostic nucleotide for the single nucleotide polymorphism which is about two to four nucleotides from the 3' terminal nucleotide of the detection primer;
b) extending the detector primer and the second primer with polymerase to produce a displaced detector primer extension product;
c) determining an efficiency of detector primer extension, and;
d) detecting the presence or absence of the single nucleotide polymorphism based on the efficiency of detector primer extension.

REMARKS

Claims 1-24, 55-61 and 63 are in the present application.

In order to advance prosecution and further clarify the present invention, Applicants have amended Claims 1, 14, and 20 and added new Claim 63, which is fully supported by the Specification. Applicants address the rejections under 35 U.S.C. Section 103 below.

I. Obviousness - 35 U.S.C. § 103 (a)

A. Claims 1-5, 7-19, 24, 55-57 and 59 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Newton et al (U.S. Patent No. 5,595,890) in view of Walker et al (Nucleic Acids Research, 1992, 20(7):1691-1696) and Krausa et al. (Human Immunology, 1995, 44:35-42). It was asserted that Newton discloses all aspects of the rejected claims except (a) that the diagnostic nucleotide of the detector primer is one to four nucleotides from the 3' terminal nucleotide of the detector primer and (b) a second primer which, upon extension, displaces the detector primer. It was then asserted that Walker et al. teach such a second primer and that Krausa et al. teach a diagnostic primer comprising a diagnostic nucleotide about one to four nucleotides from the 3' end.

In order to advance prosecution, Applicants have amended Claim 1. Specifically, the amended Claim 1 now sets forth that the method of Claim 1 must be carried out under isothermal conditions. Support for this limitation can be found on Page 6, Lines 25-36 and Page 7, Lines 1-14.

Newton et al.do not teach or suggest the subject matter of Claim 1 since Newton et al.do not teach the use of a second upstream primer to displace the detector primer under isothermal conditions. With respect to the Examiner's assertion that it would have been obvious for one of ordinary skill to combine the method of Newton et al. with the use of a second primer to displace the detector primer under low temperature (37 Degrees C), isothermal conditions as taught by Walker et al., Newton et al. warn against the use of isothermal conditions at low temperatures, and thus teach away from the claimed invention, because such conditions are likely to lead to the generation of artefactual products arising from extension of the detector primer even in the presence of a mismatched diagnostic nucleotide:

> It will be appreciated, however, that in certain circumstances synthesis of a diagnostic primer extension product might be induced to occur even in the presence of a non-complementary 3'-terminal residue. This artefactual result may arise from the use of too low a temperature in which case the temperature may be increased (Col. 11, Lines 52-57, Newton et al.)...A major source of artefactual products is probably allowing a reaction temperature to fall too low, thus permiting too low stringency, for example by removing the reaction mixture from the heat cycling means, even briefly ....(Col. 11, Lines 64-67 to Col. 12, Line 1, Newton et al.).

In addtion, Walker et al note that "considerable non-specific priming surely occurs at the 37 Degrees C reaction temperature" (P. 1695, right column, third full paragraph). Furthermore, Walker et al demonstrate that considerable non-specific background products are produced in SDA which employs the displacement of a downstream primer by extension of the upstream primer. (P. 1694 left hand column to P. 1695 right hand column, and Figure 4). These results suggest the application of the diagnostic primers of Newton et al. to the isothermal conditions of SDA would result in synthesis of artefactual products as described above by Newton et al. In addition, the suggestion by Newton et al., noted above (Col.11, Line 57), that a solution to the production of artefactual products is to increase the temperature (was practiced by Walker et al., P.1695, bottom of third full paragraph) but is subject to the further restriction in SDA that the temperature increase must be compatible with the stability of the SDA enzymes.

In view of these results, one of ordinary skill in the art would not have been motivated to combine the methods of Newton et al. and Walker et al. because the expectation of success resulting from this combination would have been low, and

Krausa et al. add no further relevant teachings. Thus, it is respectfully submitted that one of ordinary skill in the art would not find the claimed invention to be obvious from the teachings of Newton et al. and Walker et al.

B. Claims 6 and 58 were rejected under 35 U.S.C §103(a) as being obvious over Newton et al. and Walker et al. as applied to Claims 1 and 55, and further in view of Reynolds (U.S. Patent No. 5,763,14) and Mullis et al. (U.S. Patent NO. 4,683,195).

Newton et al. and Walker et al. do not teach or suggest the claimed invention. Applicants respectfully submit that Reynolds and Mullis et al. are secondary references which add no further teachings which would enable one of ordinary skill in the art to achieve the claimed invention.

C. Claims 20, 21, 60 and 61 were rejected under 35 U.S.C §103(a).as being obvious over Newton et al. and Walker as applied to Claims 1 and further in view of Chen et al (Nucleic Acids Research, 1997, 25(2): 347-353).

For the same reasons provided above, Applicants respectfully submit that the additional teachings of the secondary reference Chen et al. do not enable one of ordinary skill in the art to achieve the claimed invention.

D. Claims 22 and 23 were rejected under 35 U.S.C §103(a).as being obvious over Newton et al. and Walker as applied to Claims 1, and further in view of Thomas et al. (U.S. Patent No. 6,025,130).

For the same reasons provided above, Applicants respectfully submit that the additional teachings of the secondary reference Thomas et al. would not enable one of ordinary skill in the art to achieve the claimed invention.

Accordingly, Applicants respectfully request withdrawal of the present rejections under Section 103.

II. Conclusion

The claims of the present application are believed to be in condition for allowance, and early notice thereof is respectfully requested. Attached hereto is a marked-up version of the changes made to the claims on the attached page entitled "Version with markings to show changes made".

Respectfully submitted,

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"Version with Markings To Show Changes Made"

IN THE CLAIMS:

Claims 1, 14 and 20 have been amended as follows:

1. (2x Amended) A method for detecting a single nucleotide polymorphism in a target comprising, under isothermal conditions:

a) hybridizing a detector primer and a second primer to the target such that extension of the second primer by polymerase displaces the detector primer from the target sequence, wherein the detector primer comprises a diagnostic nucleotide for the single nucleotide polymorphism which is a 3' terminal nucleotide of the detector primer or about one to four nucleotides from the 3' terminal nucleotide of the detection primer;

b) extending the detector primer and the second primer with polymerase to produce a displaced detector primer extension product;

c) determining an efficiency of detector primer extension, and;

d) detecting the presence or absence of the single nucleotide polymorphism based on the efficiency of detector primer extension.

14. (Amended) The method of Claim 13 wherein the amplification reaction is selected from the group consisting of SDA, 3SR, NASBA, and TMA [~~and PCR~~].

20. (Amended) The method of Claim 19 wherein the label is a fluorescent donor/quencher dye pair and an increase [~~a decrease~~] in donor dye fluorescence is detected as an indication of the presence of the single nucleotide polymorphism.